European Journal of Medicinal Chemistry 60 (2013) 29–41

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Structure-based design, synthesis and evaluation of novel anthra[1,2-*d*]imidazole-6,11-dione derivatives as telomerase inhibitors and potential for cancer polypharmacology

Chun-Liang Chen [a], Deh-Ming Chang [a,c], Tsung-Chih Chen [a], Chia-Chung Lee [a], Hsi-Hsien Hsieh [e], Fong-Chun Huang [e], Kuo-Feng Huang [f], Jih-Hwa Guh [g], Jing-Jer Lin [e,h,**], Hsu-Shan Huang [a,b,d,*]

[a] *Graduate Institute of Life Sciences, National Defense Medical Center, Taipei 114, Taiwan*
[b] *School of Pharmacy, National Defense Medical Center, Taipei 114, Taiwan*
[c] *Rheumatology/Immunology/Allergy, Tri-Service General Hospital, National Defense Medical Center, Taipei 114, Taiwan*
[d] *Department of Pharmacy Practice, Tri-Service General Hospital, National Defense Medical Center, Taipei 114, Taiwan*
[e] *Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei 112, Taiwan*
[f] *Chi-Mei Medical Center, Tainan 710, Taiwan*
[g] *School of Pharmacy, National Taiwan University College of Medicine, Taipei 100, Taiwan*
[h] *Institute of Biochemistry and Molecular Biology, National Taiwan University College of Medicine, Taipei 100, Taiwan*

ARTICLE INFO

Article history:
Received 24 August 2012
Received in revised form
12 November 2012
Accepted 22 November 2012
Available online 29 November 2012

Keywords:
Telomerase
Imidazole-fused anthraquinones
TRAP assay
SEAP assay
Polypharmacology

ABSTRACT

A series of anthra[1,2-*d*]imidazole-6,11-dione derivatives were synthesized and evaluated for telomerase inhibition, *hTERT* expression and suppression of cancer cell growth *in vitro*. All of the compounds tested, except for compounds **4**, **7**, **16**, **24**, **27** and **28** were selected by the NCI screening system. Among them, compounds **16**, **39**, and **40** repressed *hTERT* expression without greatly affecting cell growth, suggesting for the selectivity toward *hTERT* expression. Taken together, our findings indicated that the analysis of cytotoxicity and telomerase inhibition might provide information applicable for further developing potential telomerase and polypharmacological targeting strategy.

Crown Copyright © 2012 Published by Elsevier Masson SAS. All rights reserved.

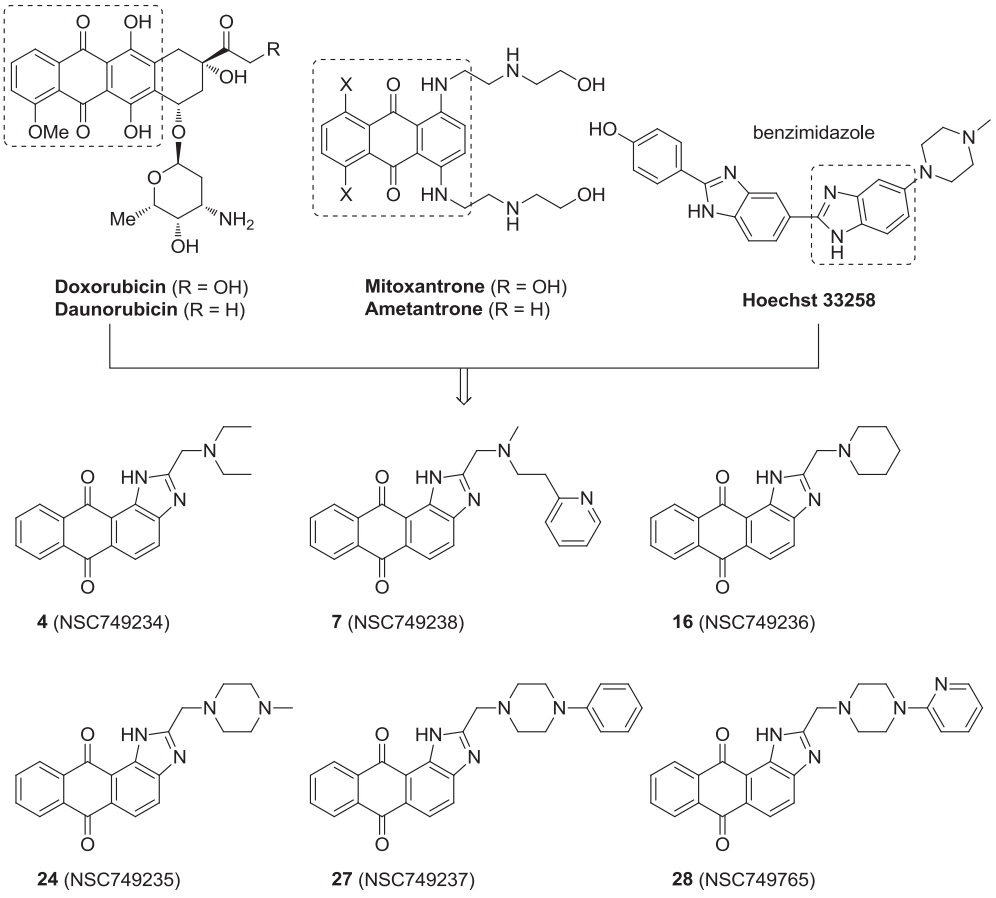
1. Introduction

The anthracycline antibiotics daunorubicin, doxorubicin, mitoxantrone and ametantrone have been shown to process strong antiproliferative properties and clinically used to treat various cancers for many decades (Scheme 1) [1]. Recent studies illustrated anthracycline antibiotics might interrupt telomere maintenance through interfering the targeting of telomerase onto telomeres [2]. Telomeres are guanine-rich DNA sequences coated by specialized proteins at the terminal ends of eukaryotic chromosomes [3,4] which consists of hexameric TTAGGG repeats sequences in human cells [5]. Telomerase is a ribonucleoprotein that consists of a catalytic subunit (human telomerase reverse transcriptase, *hTERT*) and a template RNA (human telomerase RNA component, hTERC) to add telomere repeats to the 3′ single-strand overhang [6]. Extension of telomeres by telomerase is required for un-limited proliferation of most of the immortal and cancer cells [7,8]. The important roles of telomerase in cellular immortalization have made telomerase as a potentially molecular target for cancer therapeutic discovery which might have minimal side effects [9,10]. Moreover, the anthracycline antibiotics inhibit telomerase activities through the stabilizing of G-quadruplex structure sequences. It is also well accepted that human cancer cells achieve immortalization in large part through the illegitimate activation of telomerase expression [11,12]. Therefore, agents that suppress *hTERT* expression might further develop potential telomerase and polypharmacological targeting strategy.

Based on our previous studies, some of the 1,2-heteroannelated substitution on the anthraquinone and anthra[1,2-*d*]imidazole-

* Corresponding author. Department of Pharmacy Practice, Tri-Service General Hospital, National Defense Medical Center, Taipei 114, Taiwan. Tel.: +886 2 87923311x17327; fax: +886 2 87923169.
** Corresponding author. Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei 112, Taiwan. Tel.: +886 2 28267000x5603; fax: +886 2 28267258.
E-mail addresses: jjlin@ym.edu.tw (J.-J. Lin), huanghs@ndmctsgh.edu.tw (H.-S. Huang).

0223-5234/$ – see front matter Crown Copyright © 2012 Published by Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2012.11.032



Scheme 1. Design of new compounds through hybridization of bioactive chromophoric anthraquinones (anthracycline antibiotic anticancer agents) and benzimidazole.

6,11-dione scaffold homologs might be interesting for cytotoxicity toward cancer cells or cancer polypharmacology [13]. Previous SARs studies have also shown that both anthraquinone-based compounds and bis-benzimidazole derivatives (Hoechst 33258) are known telomerase inhibitors or G-quadruplex stabilizers [14–16]. In the past, we also reported several results concerning the discovery of new classes of anthraquinone-linked heterocyclic derivatives [13,17–22]. Herein, we continue our efforts to develop an efficient synthetic procedure for the preparation of a novel series of *N*-substituent derivatives in the vacant 2-position of imidazole ring of anthra[1,2-*d*]imidazole-6,11-diones. In the series of designed analogs, we maintained benzimidazole as the central structure moiety since it was considered as the primary pharmacophore for potential telomerase inhibitory activity. Lead optimization were then focused on varying of other substituent moiety at the 2-position of the imidazole skeleton, by adding electron-withdrawing or electron-releasing substituents. These compounds were evaluated for cytotoxicity by MTT assay or sulforhodamine B assay (SRB assay) on non-small lung cancer cell, H1299, prostate cancer cells PC-3 [23–26], as well as telomerase inhibition using TRAP assay [27,28] and SEAP assay [29,30]. Finally, the interplay between the cytotoxicity, *hTERT* repressing activities and the drug explains the SARs of derivatives and the molecular basis of drug-induced activities.

2. Chemistry

There has been continuing interest in the synthesis of anthra[1,2-*d*]imidazole-6,11-dione derivatives and their systematic dissection largely on account of their biological activities [13]. The method for constructing the core structure of the compounds is outlined in Scheme 2. The synthesis commences starting from 1,2-diaminoanthraquinone, the cyclization with chloroacetyl chloride formed compound **1**. The preparation of compounds **2**–**33** involved direct amination using various amines and TEA/DIPEA in THF to obtain our desired derivatives. As shown in Scheme 2, compound **34** was prepared by amination between 1,2-diaminoanthraquinone and 3-chloropropionyl chloride in the presence of pyridine. The resulting compounds were further cyclization converted to compound **35** that has a terminal chloroethyl group attached to the imidazole-fused ring. Treating compound **35** with various amines in DIPEA/THF gave the desired compounds **36**–**40** through nucleophilic substitution of the chlorine atom by appropriately substituted piperazine. The ^{13}C NMR data showed that the signal for carbonyl group on the core structure of anthraquinone was at the range δ 182–185 ppm whereas the signal of imidazole ring was at δ 154–161 ppm, respectively. Besides, all the final products were monitored by TLC; the quantities of the byproducts were separated from their physical chemistry properties and purification by tedious recrystallization and chromatography. All of the structural compounds were determined by ^{1}H NMR, ^{13}C NMR and high resolution mass (HRMS) spectra and the results are presented in the experimental part.

3. *In vitro* anti-proliferative activities

As reported in previous sections, all of the newly synthesized compounds were evaluated for their effects on cell viability in H1299 cell (Table 1). We found that most of the tested compounds showed cytotoxicity toward H1299 cells at micromolar ranges.

Download English Version:

https://daneshyari.com/en/article/1399257

Download Persian Version:

https://daneshyari.com/article/1399257

Daneshyari.com